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Physicochemical characterization and antioxidant properties of cerium oxide nanoparticles

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Abstract. Studies of the biological activity of cerium oxide nanoparticles (CONPs) show that this compound exhibits antioxidant, antitumor, antibacterial and antiviral properties. The CONPs were obtained by pulsed electron evaporation in a low-pressure gas with a specific surface area of ~ 190 m^2/g. Strongly-noequilibrium conditions of synthesis led to the formation of high defect structures, which makes it possible to change the Ce^{3+}/Ce^{4+}ions ratio and, consequently, to enhance the level of their biological activity. To analyze the content of cerium with different valences, X-ray photoelectron spectroscopy was performed. To determine the enzyme-like activity of CONPs, a chemical analysis of the interaction with hydrogen peroxide was carried out on a spectrophotometer. The results show a significant presence of Ce^{3+}in CONPs and the inhibition of reactive oxygen species (ROS). The valence of the cerium atoms determines the chemical activity of CONPs; thus, in a more alkaline medium, the CONPs decrease the ROS concentration, while in the acidic medium its activity diminishes. By varying the parameters of the nanopowders obtained and achieving the optimum Ce^{3+}/Ce^{4+} ratio, one can produce CONPs having properties which enable the creation of pharmaceuticals for protection against ROS or for combating tumors, viruses and bacteria.

1. Introduction

Nanoparticles of cerium oxide (CONPs) are a promising object for various biomedical applications. Numerous studies have shown that this compound manifests antioxidant, antitumor, antibacterial and antiviral properties, which testify to the prospects of its use in pharmaceutics [1-3]. Significant interest in the study of this object is a result of the fact that, upon transition to the nanoscale state, oxygen non-stoichiometry arises and, on the surface of the nanoparticle, the Ce^{4+} ions are reduced to the Ce^{3+} state. Such oxygen non-stoichiometry correlates with the catalytic activity of CONPs and is thought to be responsible for their unique biological activity. In addition, it was discovered that the change in the Ce^{3+}/Ce^{4+} valence ratio in the nanoparticles correlates with the change in their biological activity [4].

It should be noted that the method used for obtaining nanoparticles has a significant effect on their physicochemical properties. When CONPs are produced on the NANOBIM-2 installation [5-7] by evaporation of a pulsed electron beam in a low-pressure gas, one can obtain a narrow particle size

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distribution with a high specific surface area, with the formation of a large number of defects in the crystal lattice of nanoparticles. Moreover, the radiation defects, produced by exposure to the deceleration radiation of the evaporating electron beam, increase the defect content in the material. An additional feature of this method is the production of mesoporous nanopowders (NPs), which allows them to be used for drug delivery in the same way as nanorods [6].

The present paper is devoted to studying the electronic structure of CONPs obtained by pulsed electron evaporation with the aim of determining the Ce^{3+}/Ce^{4+} valence ratio and establishing a correlation between the physicochemical properties of the compound and the biological activity manifested by it.

2. Materials and methods

Morphology studies and phase analyses were carried out with the transmission electron microscope JEM 2100F (Schottky cathode, using a 200 kV electron beam). Electron diffraction patterns were simulated by the JEMS software. The sample was prepared by placing a drop of a sonicated solution of the sample in ethyl alcohol on a holey carbon coated copper grid. Subsequently it was dried in the air.

The X-ray photoelectron spectra (XPS) were taken on an ESCALABMKII electronic spectrometer using Mg K R (1253.6 eV) as the excitation source. The samples were CONPs tablets with a diameter of 4.5 mm, pressed at a pressure of 2000 MPa. The spectra were analyzed using the XPSPEAK version 4.1 software package. The obtained spectra were compared with the data [8] to determine the ratio of the two valences of cerium. Quantity of ions Ce^{3+} and $Ce^{4+}$was determinated by means of the electronic 3d levels. Ce^{4+} has peak in the area 917 eV which is absent in Ce^{3+} range. The area under all peaks of Ce^{3+} and Ce^{4+} was defined by ratios of two valence states of cerium. Then the percentage to the general range paid off.

The UV/vis absorption spectra were measured on a 9423UVA1002E Helios Alpha spectrophotometer (Thermo Fisher Science); the time dependence curves of optical density were measured on a PE-5300 (Ecohim) spectrophotometer. The photoluminescence spectra were measured with a xenon lamp as the excitation source and recorded with MDR-23 monochromator and FEU-106 photoelectric multiplier. To analyze the enzyme-like activity, we performed the measurements of the optical density dynamic change of the CONPs suspensions with a concentration of 200 μg/ml at a wavelength of 380nm before and after the addition of hydrogen peroxide. CONPs suspensions were stabilized by sodium citrate in a ratio of 1:1 and sounded in the PSB-Gals ultrasonic bath for 20 minutes. The time dependence curves of optical density were measured on a PE-5300 (Ecohim) spectrophotometer. All the measurements were performed at room temperature. To change the pH, citric acid and sodium hydroxide were added to the medium. The acidity of the medium was monitored with a pH meter KELILONG PH-009. The optical density were measured in the Eppendorf UVette routine pack cuvette through a 10 mm window, with permeability in the range of 220-1600 nm. After measuring the optical density of the suspension, 20 μl of hydrogen peroxide was added to the cuvette and the measurements were started.

3. Results

3.1. HRTEM/FFT

HRTEM analyses revealed the morphology of the studied nanoparticles system. The system was composed of nanoparticles of a typical size of up to 5 nm, formed with a CeO_2 cubic phase (a=5.45Å; SG 225). Most of the nanoparticle surfaces were formed with the facets {1,1,1} and {0,0,1}, i.e., crystallographic planes with high electron density (figures 1 and 2).

Table 1. Coefficients of reaction of the ROS inhibition.

pH	3	5	6	7	9	10
K (min^{-1})	0.002	0.026	0.085	0.095	0.150	0.162

The greater part of the oxygen vacancies are present in the {1,1,0} and {1,0,0} planes. Thus, the main active portion of NPs is isolated from the environment and does not actively enter into chemical reactions.

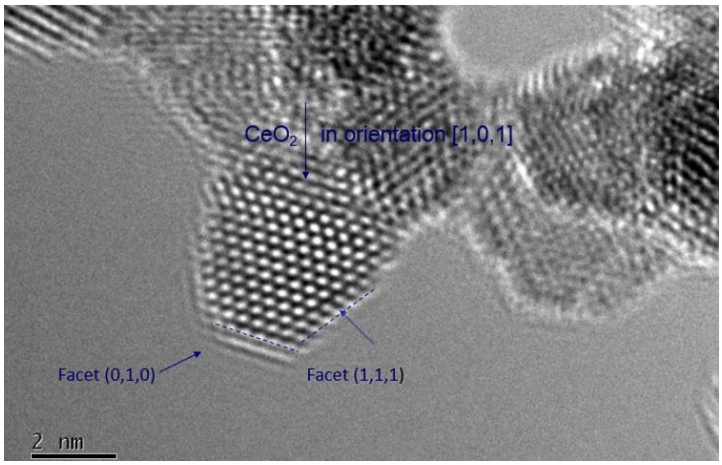

Figure 1. TEM picture of the CONPs.

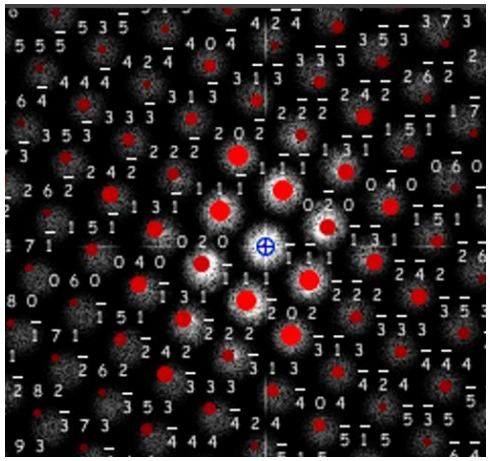

Figure 2. FFT is evaluated on CeO_2 lattice in the crystallographic orientation {1,0,1}.

3.2. XPS analysis

Analysis of the panoramic photoelectron spectra shows the presence of divalent states of cerium in the NP (figure 3). In the XPS spectrum of cerium ions in CONPs, the peaks of $Ce^{3+}3d_{3/2}$ (at binding energies of 899.7 and 904.2 eV) and Ce^{3+} $3d_{5/2}$ (881.5 and 885.9 eV) are relatively strong. This indicates that the Ce^{3+} ions are located on the surface of CONPs. The estimated density of ions Ce^{3+} in the sample is 32% from the total volume, ions Ce^{4+} − 68% (figure 4).

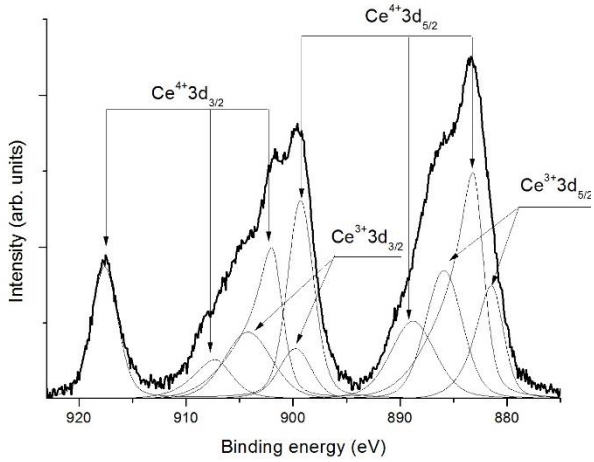

Figure 3. XPS analysis of the CONPs. Peaks of electronic levels Ce^{3+} and Ce^{4+}.

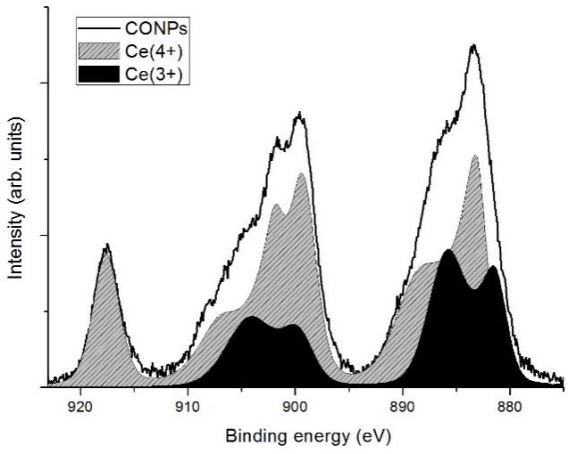

Figure 4. XPS analysis of the cerium oxide NPs. Area under the spectrum Ce^{3+} and Ce^{4+}.

The Ce^{3+}/Ce^{4+}ratio in crystallites is highly dependent on synthesis conditions and ambient exposure. The XPS clearly demonstrates the presence of trivalent cerium in NPs obtained by the physical method. Stabilization of these samples with a significant amount of Ce^{3+} on the surface has

not been studied. The stabilization of cerium oxide NPs with a large number of trivalent atoms, while preserving the Ce^{3+}/Ce^{4+}ratio, is a difficult problem.

3.3. Optical properties and luminescence

Figure 5 shows the optical absorption spectrum of the CONPs suspension (the CeO_2 concentration is 200 μg/ml). In the region of 500-800 nm, no significant absorption is observed, and the optical transmission of the sample is at least 80%. In the 200-500 nm region, a broad intense absorption band is observed with a maximum in the 300-320 nm region. Based on the edge of the main optical absorption band, it is possible to determine the band gap E_g of the nanocrystal [9-10]. The width of the band gap was calculated using the Tauc plot method [11]. The calculated values of E_g for direct and indirect transitions are 3.4 and 2.3 eV, respectively.

Figure 6 shows the spectra of photoluminescence (PL) and PL excitation of the CONPs. It can be seen from the figure that in the visible region the luminescence spectrum is represented by a wide (300-600 nm) non-elementary PL band with a maximum of 400 nm. The PL excitation spectrum is represented by a broad band in the 220-300 nm region with a maximum of 280 nm and correlates with the UV part of the optical absorption spectrum of the NP suspension (figure 5). The results of the PL spectrum decomposition (figure 6) indicate the presence of three overlapping elementary bands.

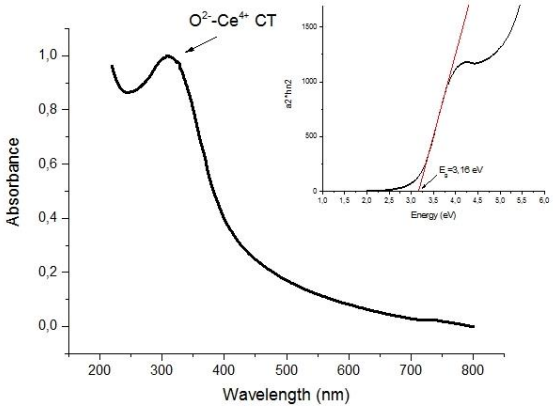

Figure 5. Optical absorption spectrum of the CONPs suspension (the CeO_2 concentration is 200 μg/ml).

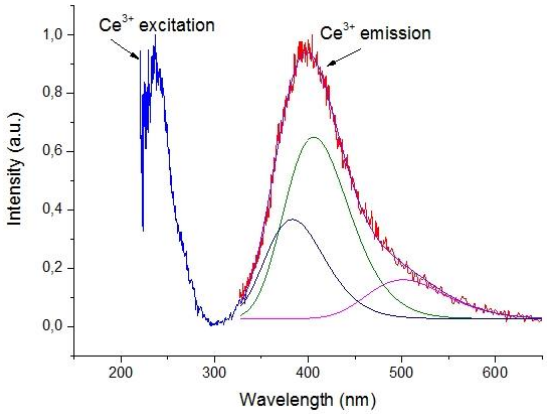

Figure 6. Spectra of photoluminescence (PL) and PL excitation of CONPs.

3.4. Study on redox enzyme-mimicking activities

Hydrogen peroxide (H_2O_2) is one of the reactive oxygen species (ROS) which arise as a result of the interaction of ionizing radiation with matter. ROSs make a significant contribution to the death of cells from radiation. CONPs are able to perform a catalase function that inhibits ROS. The enzyme-like mechanism of the action of CONPs can be represented in the form of chemical degradation [3].

The process proceeds in several stages, as a result of which oxidation of cerium oxide occurs, followed by regeneration to the initial state. In the aqueous solution of CONPs at pH>6, cerium monoperoxy-trihydroxide is formed as an intermediate product, which then decomposes to the initial state [3]. The resulting compound can be recorded by measuring the absorbance of the suspension at a wavelength of 380 nm.

The obtained dependencies in the figure 7 of the CONPs suspensions allow for evaluation of the ongoing chemical reactions in the samples. When hydrogen peroxide is added, the absorption in range 380 nm increases due to an increase in the concentration of the dark crystal of cerium monoperoxy-trihydrate. Moreover, maximum absorption is observed in samples with an alkaline medium. Besides, in a more alkaline medium, the reaction proceeds during the entire observed time interval, while in the acidic one the reaction slows down already after an hour.

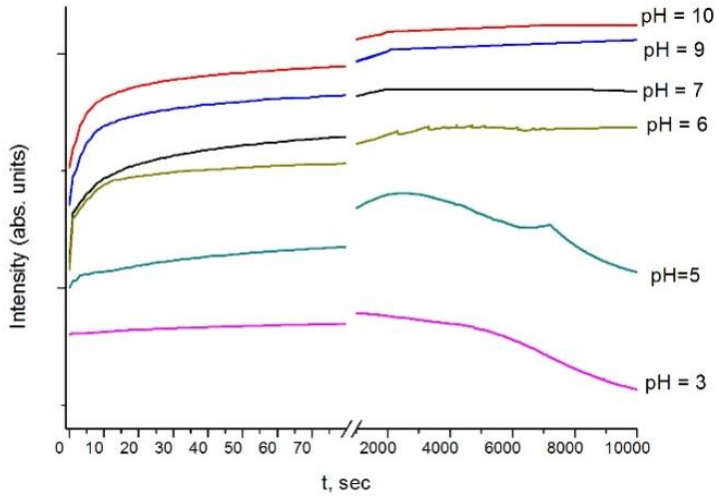

Figure 7. Dynamics of the change in optical density of the 200 μg/ml CONPs suspension (the wavelength is 380 nm), depending on the pH of the solution.

Table 1 shows the reaction rates of the ROS inhibition reaction. The growth coefficient increases significantly at pH>6 and doubles when the pH equals 10. It is seen from figure 7 that the reaction proceeds in several stages with the formation and decomposition of cerium monoperoxy-trihydrate. In an alkaline medium, a large increase in the concentration of the crystal is observed throughout the time interval. However, in a medium with a pH of less than 5, the crystal concentration decreases after 35 minutes after the addition of hydrogen peroxide.

4. Discussion

The obtained results of TEM and XPS clearly demonstrate the presence of oxygen non-stoichiometry and a large number of Ce^{3+} ions. As a result, it can be concluded that, on the surface of nanoparticles, oxygen vacancies are present, which interact actively with the matter.

Comparing the obtained results and the XPS spectra of the cerium nanoparticles obtained by the chemical method [12], it can be concluded that the initial NPs produced on an electric power source contain a larger amount of Ce^{3+} ions. However, when the NP is doped with other metals, it is possible to increase the Ce^{3+}/Ce^{4+} ion ratio and increase the number of oxygen vacancies. Such ratio of the Ce^{3+}/Ce^{4+} ions is observed for the particles of the sizes of 3.8 ± 0.6 nm. However, the amount of Ce^{3+} ions is smaller than in the samples obtained by chemical methods for particles smaller than 3 nm [3]. It is possible to attain the maximum concentration of trivalent cerium ions by decreasing the grain size to 1.1-1.3 nm [12].

Analysis of the luminescent properties of CONPs (figures 5 and 6) also testifies to the presence of cerium ions in different valence states. The observed luminescence of the CONPs in the visible region of the spectrum is due to radiative transitions in the Ce^{3+} ion. The final stage of the radiative process is described by the scheme: $(Ce^{3+})^* \rightarrow Ce^{3+}+h\nu$. In addition, a weak band is observed in the PL spectrum in the region of 2.5 eV, which can be associated with the emission of F_0 centers connected with the formation of oxygen vacancies [13]. A wide absorption band in the region of 300-400 nm (figure 5) should be attributed to photo induced optical transitions with charge transfer from the 2p orbital of oxygen to the unfilled 4f orbital of the Ce^{4+}ion according to the scheme: $Ce^{4+}+O^{2-} \rightarrow Ce^{3+}+O^{-}$ [14].

It was found that, in the interaction of CONPs with hydrogen peroxide, a dark crystal of monoperoxy-trihydrateis produced which actively increases the absorption of the suspension at a wavelength of 380 nm. Eventually, monoperoxide breaks down and cerium returns to its original state. However, in an acidic medium less than 5, cerium cannot change into a trivalent state.

CONPs actively inhibit ROS at pH>7, but the rate of these reactions decreases in a more acidic medium as shown in the figure 7 and table 1. The rate of reaction depends on many factors, including

the concentration of reagents. The concentration of Ce^{3+} ions and the specific surface of NPs remain important parameters.

The interactions of CONPs obtained at the NANOBIM-2 installations with ROS show a non-linear dependence on pH of the medium. Thus, the protective properties of CONPs will be manifested only in tissues close to neutral media, in particular, in healthy tissues.

It is known that the protective effect of CONPs for biological objects mainly consists in the chemical inhibition of ROS [2]. However, the influence of nanoscale objects is not limited only to their chemical activity. Nanoparticles of metal oxides with a high atomic number increase the LET of ionizing particles and affect the signal pathways of many kinases in cells [3]. Thus, complex studies of all the properties of CONPs and their comparative characteristics are required.

5. Conclusion

The obtained results allow the conclusion to be drawn regarding the significant presence of Ce^{3+} ions and the presence of oxygen non-stoichiometry in the CONPs produced by the methods of evaporation by a pulsed electron beam. However, a significant number of CONPs have a size of 3 to 5 nm, with a large number of Ce^{3+} ions present in the samples.

The obtained results are in agreement with the literature data that show that CONPs possess enzyme-like properties of ROS inhibition [3]. It was found that the inhibition activity depends on the acidity of the medium.

Thus, by controlling the defects and properties of CONPs, it is possible to change their biological activity for solving a wide range of problems, including their combined influence on biological objects together with other physicochemical factors.

Acknowledgments

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